DISSERTATION

PREDICTORS OF INTRACTABLE EPILEPSY IN CHILDHOOD: A CASE CONTROL STUDY

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CERTIFICATE

This is to certify that the dissertation titled **"PREDICTORS OF INTRACTABLE EPILEPSY IN CHILDHOOD: A CASE CONTROL STUDY"** submitted by Dr.SANGEETHA.P to the Faculty of pediatrics, The Tamilnadu Dr. M.G.R. Medical university, Chennai in partial fulfillment of the requirement for the award of M.D. Degree (Pediatrics) is a bonafide research work carried out by her under our direct supervision and guidance.

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This is submitted to **The Tamilnadu Dr. M.G.R. Medical University**, Chennai in partial fulfillment of the rules and regulations for the M.D. Degree Examination in Pediatrics.

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INTRODUCTION

Epilepsy is a common neurological disorder affecting 3-6/1000 children[1]. Approximately 70–80% will be controlled with single drug and 10-15% require combination chemotherapy. However 10 – 20% of epileptic patients are resistant to therapy ,the condition , so called 'intractable epilepsy'[1,3]. While a great deal is known about seizures and epilepsy, little is known about the identification and causes of intractable epilepsy[14]. Such intractable epilepsy, impose considerable socioeconomic and psychological constraint on the individual patient and casts a substantial burden on health and welfare resources. Many terms have been used for of these patients who doesn't respond to therapy, like 'treatment non responder', 'refractory', 'intractable' and 'drug resistant'. Early identification of these children prone to develop intractable seizures is critical for parental counselling, selecting patients for more intensive investigations and treatment, such as early consideration for epilepsy surgery. In addition determining risk factors for intractability may help shed some light on the causes and mechanisms underlying these drug resistant epilepsy.

Epidemiology of refractory epilepsy is complicated by several issues[14]

1) There is no unifying definition of intractable epilepsy.
2) Patient do not necessarily become refractory immediately at the time of diagnosis, nor do they inevitably remain refractory throughout the course of illness.
3) Response to medication is assessed , without a pretreatment baseline, as most patients are treated rapidly after diagnosis.
4) Sometimes some of these patients who are defined as intractable, will respond readily, although not completely to therapy.

Definitions:

Seizures:

seizure or convulsion is a paroxysmal , time limited change in motor activity and or behavior that results from abnormal electrical activity in brain[8].

Epilepsy :

Two or more unprovoked seizures occurring at an interval of more than 24 hours apart[8] .

International classification of epileptic seizures

Partial seizures

Simple partial (consciousness retained)

Motor

Sensory

Autonomic

Psychic

Complex partial (consciousness impaired)

Partial seizures with secondary generalization

Generalized seizures

Absence → Typical

↘ Atypical

Generalized tonic clonic

Tonic

Clonic

Myocolonic

Atonic

Infantile spasm

Unclassified seizures

Defining intractable epilepsy

There is no uniform consensus regarding definition of intractable epilepsy. These definition and criteria are of specific use in research purpose.

Different definitions which have been used are

1) Children who had one or more seizures per month over a period of six or more months and who had experienced trials of atleast two different antiepileptic drugs with adequate compliance [1]
2) Uncontrolled seizures that occurred with an average frequency of atleast,one per month over a period of two years and during that period, atleast three different antiepileptic drugs should have been used daily, singly or in combination[2]
3) Seizures that continue to occur despite treatment with a maximally tolerated dose of a first line antiepileptic drug as monotherapy or in atleast one combination with an adjuvant medication[6]
4) Two or more seizures per month for a period of two years or more despite supervised trials

5) Occurrence of one or more seizures per month on follow up of one year or more with an adequate trial of two primary antiepileptic drug and or more of the new antiepileptic drugs[7]

Intractable epilepsy as a disability

Epilepsy is sometimes called the invisible disability. But if one thinks in terms of people with drug responsive seizures this is not entirely correct. These people do live normal lives and reach their full potential for accomplishment in lives. Intractable epilepsy is clearly a disability. Public seizures lead to stigma, and to economic and social discrimination. There is possibility of head injury due to falls. They are not allowed to drive or to swim alone. They are told to take showers rather than baths. Their lives become limited and circumscribed. In addition, these patients with intractable epilepsy have a number of non physical disabilities, called the co morbidities. These are less well known and unfortunately seldom treated, but they are often more serious than the seizure themselves.

Aetiology of intractable epilepsy

1) Cerebral palsy

2) Neurocutaneous syndromes

3) Developmental malformations

4) Neurodegenerative / neurometabolic problems

5) Central nervous system infection sequelae.

6) Neurocysticercosis

7) Epileptic syndromes

8) Cerebral tumors

9) Mesial temporal sclerosis

10) Porencephalic cyst

11) Head injury

12) Cerebrovascular accident

13) Idiopathic.

Epileptic syndromes

West syndrome

It is a triad of infantile spasms, a pathognomonic EEG pattern called 'hypsarrythmia' and mental retardation. Onset of seizures is between the third and twelfth months of age. Three types of attacks occur – severe myoclonic convulsion, nodding attacks and salaam spells. Drugs used in treatment are ACTH and Vigabatrin[9]

Lennox – gestaut syndrome

Triad of multiple seizures, 1.5 to 2 Hz spike wave complex on EEG and mental retardation characterize this syndrome. Age of onset is between 3-5 years. Multiple types of seizures occur like atypical absence, generalized tonic, atonic and myoclonic seizures. Drugs effective are Valproate, Clonazepam, Vigabatrin, Lamotrigene etc. Seizures are very difficult to control and most children are mentally retarded by two years of age[9] .

Approach to intractable epilepsy

A detailed history has to be taken to know the type of seizures and frequency of seizures. A review of the past drug records is mandatory. Detailed clinical examination has to be done to exclude neurological deficit. A detailed neurological history and examination may give some clue to the aetiology of

intractable epilepsy. It also helps us to rule out 'pseudo intractability' – resistant seizures due to inadequate dosage, wrong drug or non-epileptic seizures. Patient should be requested to keep a seizure diary. Ideally patient must be admitted and investigated.

Differential considerations in intractable epilepsy[6]

A] Errors in diagnosis

1) Failure to identify a seizure syndrome or causative condition

2) Incorrect seizure classification (partial or generalized)

3) Non epileptic seizures (syncope, pseudo seizures)

B] Errors in drug choice or management

1) Wrong drug for the seizure type / syndrome

2) Inadequate dose

C] Poor medication compliance

1) Inadequate patient instruction or education

2) Too frequent or complex dosing schedule

3) Intolerable side effects

D] True intractability

Investigations

1) Detailed metabolic workup
2) EEG
3) Video EEG
4) Neuroimaging – MRI
   CT
   PET
   SPECT

EEG

Most commonly performed neurodiagnostic study in the evaluation of patients with seizures in EEG. Most reliable findings are primarily generalized spike and wave discharge or focal spike or sharp wave discharge over frontal or temporal lobes [6]. A normal EEG doesn't exclude the diagnosis of a seizure disorder. A prolonged EEG or serial EEGs may improve the sensitivity. Upto 2% of non seizure experiencing individuals may have potentially epileptogenic activity on their EEG.

Video EEG recording

It's an extremely helpful tool in the evaluation of intractable epilepsy. The combined use of video and EEG recording improves the sensitivity and specificity over EEG recording alone.

It has been demonstrated to accurately differentiate between epileptic and nonepileptic seizures, to distinguish between primarily generalized and partial onset seizures and to determine seizure onset localization and lateralization.

Neuro-imaging

-Magnetic Resonance Imaging (MRI)

- Computed Tomography (CT)

- Positron Emission Tomography (PET)

- Single Photon Emission Computed Tomography (SPECT)

MRI

Improves our understanding about the pathological substrates of epilepsy and also helpful in determining the long term seizure prophylaxis. In patients considered for surgical therapy, the presence of a focal neuroimaging abnormality can improve the prognosis for an excellent outcome.

MRI imaging is the imaging procedure of choice in those with intractable partial epilepsy. It has been demonstrated to be superior to CT imaging in intractable epilepsy. Some low grade malignancies, mesial temporal sclerosis, neuronal migration abnormalities and heterotopias might be missed on CT imaging which are identified by MRI.

Management

Pharmacotherapy

Selection of an antiepileptic medication is the most important decision physicians will make, after conclusion of the diagnostic evaluation. Treatment plan should be made based on the types of seizure and epilepsy and by the review of all antiepileptic drugs that have and have not been used to their maximum tolerated doses, those that may have shown some benefit, those that have not been used at all, and those that would be

appropriate to try. It is then possible to select the AED that is most likely to be efficacious and to have fewest side effects and to adjust the dose of this drug to the optimum. Antiepileptic drugs that have not aided seizure control and have produced adverse effects, should then be gradually tapered and discontinued. If seizures remain uncontrolled, other first line and second line drugs that have been identified as possibly helpful or alternative treatment should be considered [7]

Elements of successful treatment [6]

Classify seizure disorder correctly

1) Balance the maximal effective dose with minimal side effects
2) Choose dosing to maximum compliance
3) Treat the patients symptoms, not the EEG findings or the serum levels

FDA approved monotherapy[12]

Partial Seizures

- Carbamazepine
- Sodium Valproate
- Phenytoin
- Lamotrigene
- Oxcarbamazepine

Primarily generalized seizures

- Sodium Valproate
- Phenytoin
- Phenobarbitone
- Ethosuximide
- Clonazepam
- Primidone

FDA appoved adjunctive therapy

- All agents approved as monotherapy
- Gabapentin
- Topiramate
- Tiagabine
- Levetiracetam
- Felbamate

Seizure type – first choice, other options

Infantile spasm : ACTH, Vigabatrin, Topiramate

Absence seizures : Ethosuximide, Sodium Valproate, Lamotrigene

Atonic seizures : Valproate, Lamotrigene, Topiramate, Phenytoin

Myoclonic seizures : Valproate, Clonazepam, Topiramate, Lamotrigene

Alternate modes of treatment of intractable epilepsy

Ketogenic diet

This is a high fat, low protein, low carbohydrate developed in 1921. It mimics the effect of starvation[7]. The diet consists of 60% medium chain triglycerides, 11% long chain saturated fat, 10% protein & 19% carbohydrate.

Ketogenic diet causes a prompt elevation of plasma ketone bodies that the brain uses as an energy source. It is most effective in infants and children with intractable seizures. The mechanism of action is not estabiiashed. It is effective for the control of myoclonic seizures, infantile spasms, atonic seizures and mixed seizures of Lennox-Gestaut syndrome[7,9]. The side effects are abdominal pain and diarrhea.

Vagal nerve stimulaton

Those patients who are medically refractory and are not candidates for brain surgical procedure may be evaluated as potential candidates for vagal nerve stimulation. At present, it is only approved for the treatment of medically

refractory partial epilepsies in patients who are > 12 years of age and are not surgical candidates [6]

It utilizes a programmed stimulus from a chest implanted generator via coiled electrode tunelled to the left vagus nerve[9]. Approximately 1/3rd of those treated with vagal nerve stimulation have a greater than 50% reduction in their seizure frequency. Another 1/3rd have less than 50% reduction in seizure frequency and the remaining 1/3rd have no improvement. There are minor side effects like neck pain, hoarseness and brief cough. Drawbacks are the need for surgical implantation and its high cost.

Surgical treatment

In intractable epilepsy, surgical resection of the focal epileptogenic cortex is the most effective method currently available to render children and adults seizure free. Potential candidates include patients with intractable seizures, who have seizures emanating from a localized region of brain that can be resected without neurological morbidity. Indications include mesial temporal sclerosis, heterotopias, and surgically remediable syndromes. A comprehensive pre surgical evaluation is necessary to pinpoint the seizure onset site and to identify risk of neurological morbidity. These include ictal video EEG monitoring, brain imaging, neuropsychological and speech language studies [6]

The surgical procedures available are

1) Hemispherectomy
2) Interhemispheric commissurotomy
3) Temporal lobectomy
4) Lesionectomy
5) Multilobar resection

1] Hemispherectomy

Exclusively for children with intractable epilepsy with hemiplegia. Best results are for children with disease affecting only one hemisphere, like Sturge Weber syndrome and Rasmussen encephalitis. The original procedure consisted of removing the cortex of one hemisphere along with variable portion of the underlying basal ganglia. Modified procedure includes removal of most of the damaged hemisphere, but with portions of frontal and occipital lobe kept in place, but disconnected from other hemisphere and brainstem [9]. Complications are hemorrhage and hydrocephalus.

2] Interhemispheric commissurotomy

It includes disconnecting the hemisphere from each other and from the brainstem. It is an alternative to hemispherectomy in children with intractable epilepsy and hemiplegia. Another use is to decrease occurrence of secondary generalized tonic clonic seizures from partial seizures. Two types are there – complete and partial commisurotomy. Side effects are hemiparesis, mutism, apraxia and urinary incontinence.

3] Temporal lobectomy

It is the most common surgical procedure performed for medically intractable epilepsy [6]. Complete seizure relief should be attainable in more than half of the children with intractable partial complex seizures of temporal lobe origin[9]. Only children who have a unilateral temporal lobe focus (mesial temporal sclerosis) are candidates for surgery. Surgical procedures include resection of superior temporal gyrus, hippocampus and amygdala. The most common complications are superior quadrantanopia, aphasia, but they are transitory.

REVIEW OF LITERATURE

Etiology & clinical predictors of intractable epilepsy:

Chawla et al conducted this case control study comprising 50 cases and 50 control subjects in Kalawati Saran Children's hospital, New Delhi. Patients included children who had more than one seizure per month over at least 6 months. Control subjects included children with epilepsy who had been seizure-free for more than 6 months. Patients were evaluated with special reference to birth history and development. Clinical examination and neurodevelopmental assessment were performed in all the patients. Drug monitoring was performed to exclude pseudointractability. Epilepsy in the study group was caused by perinatal problems (48%) and sequelae of central nervous system infection (24%) and was idiopathic in 20%. In the control group, epilepsy was idiopathic in 72%, a result of calcified granuloma in 22%, and perinatal problems comprised 6% of the subjects. On univariate analysis, strong association was evident between intractable epilepsy and several factors, including age at onset of seizure, remote symptomatic epilepsy, initial seizure type, history of neonatal seizure, high initial seizure frequency, microcephaly, and neurologic impairment. On multivariate analysis, neurologic impairment (odds ratio [OR] 12.25; 95% confidence interval [CI] 3.58-41.89), age at onset of seizure less than 1 year (OR 11.70; 95% CI 2.95-46.43), myoclonic seizure/infantile spasm

(OR 10.36; 95% CI 2.39-44.93), and remote symptomatic epilepsy (OR 2.9; 95% CI 1.13-7.43), were independent predictors of intractability.

Predictors of intractable epilepsy in childhood; a case control study:

This case control study was done by Berg et al in the department of paediatrics and neurology, Yale university, New Haven, Connecticut.Cases were children who had an average of one seizure or more a month over a 2-year period and who, during that time, had failed trials of at least three different antiepileptic drugs. Controls were children who had epilepsy, who had been seizure-free for >2 years, and who had never, before becoming seizure-free, met the definition for intractable epilepsy. Strong univariate associations were noted between intractability and several factors: infantile spasms (IS), remote symptomatic epilepsy, a history of status epilepticus (SE) before the diagnosis of epilepsy, neonatal seizures, and microcephaly. Cases were significantly younger than controls at onset (1.8 vs. 5.8 years); this was not due solely to cases with onset during the first year of life but was an association apparent throughout the age range studied. With multiple logistic regression,

independent predictors of intractability were infantile spasms , odds ratio (OR) = 10.42, $p = 0.03$; age at onset with a decreasing risk with increasing age, OR = 0.77 per year, $p < 0.0001$; remote symptomatic epilepsy, OR = 2.24, $p = 0.04$; and SE, OR = 3.30, $p = 0.04$.

Risk factors predicting refractoriness in epileptic children with partial seizure:

This retrospective study was done by Sakir et al in the department of paediatric neurology, Cukurova university, Adana, Turkey. Fifty children with intractable epilepsy as evidenced by at least 1 epileptic fit per month were included in the study group, whereas the control group consisted of children who did not experience any recurrent seizure for at least 1 year at the time of the study. Chi square test test was used to evaluate the relationship between the test variables for the 2 groups, and the estimated relative risk (odds ratio) for each variable was calculated. The risk factors were subsequently determined by logistic multiple regression analysis. Univariate analysis showed that mental retardation, neurological abnormality, neuroradiological abnormality, perinatal anoxia, neonatal convulsion, presence of status epilepticus, and symptomatic etiology were significant risk factors for the development of refractory epilepsy ($P < .05$). For multivariate logistic regression analysis, age at seizure onset, status epilepticus, mixed type of seizures, and history of frequent seizures (more than once a month) were all found to be significant and independent risk factors for refractory epilepsy, and the number of drugs used in the study group was significantly higher than that in the control group ($P < .05$). In line with these findings, it was concluded that children who present with epilepsy and have these risk factors should be referred to a center where epileptic surgery is carried out without delay.

Profile of intractable epilepsy in a tertiary referral centre

Singhvi et al did this study in the department of neurology, institute of medical education and research, Chandigarh in 100 patients over 14 months. Detailed history, examination, investigatons like EEG, CT scan and details regarding pharmacotherapy were analysed. Factors which predicted poor prognosis were found to be organic brain lesions, partial seizures, multiple seizure types, high seizure frequency, seizure onset in infancy and abnormal EEG.

Predictive factors in pediatric intractable seizures

Javad akhondian et al conducted this case control study in Children's neurology clinic of Imam Reza hospital in north eastern Iran with 51 cases and 80 controls. 'Intractable seizure' was defined as seizure frequency of atleast one attack per month during six months, despite receiving two antiepileptic drugs. 'Well controlled seizures' was defined as no seizure episode during six months after the start of treatment. Factors affecting the occurrence of refractory seizures with a p value < 0.05 were found to be age < 1 year, multiple seizures, male gender, myoclonic seizures, neurological deficit, neonatal seizures, abnormal EEG and CT.

Epidemiology and etiology of intractable epilepsy in Qatar

Al Hail et al conducted this study in Hamad medical corporation, Doha, Qatar. The medical records of 219 patients seen over a period of eight years were reviewed to determine incidence and causes of intractable epilepsy. Out of these only 39 patients fulfilled the criteria of intractable epilepsy. Intractable epilepsy was defined as occurrence of ≥ 2 seizure per month despite receiving adequate mono or polytherapy of AED medication for at least two years. The most common type of intractable epilepsy was idiopathic generalized epilepsy(75%), followed by symptomatic epilepsy(19%), and temporal lobe epilepsy(6%).

Early development of intractable epilepsy in children: a prospective study

Berg et al conducted this prospective study in Northern Illinos University. Children with newly diagnosed epilepsy were prospectively followed up for occurrence of intractable epilepsy. Out of 599 children followed up, 60 children(10%) have met the criteria for intractable epilepsy, including 34.6% with cryptogenic/symptomatic generalized , 2.7% with idiopathic, 10.7% with other localization related and 8.2% with unclassified epilepsy. Epilepsy syndromes, initial seizure frequency($p<0.0001$), focal EEG

slowing(p=0.02), and neonatal status epilepticus(p=0.001) were associated with an increased risk of intractable epilepsy

If a first antiepileptic drug fails to control a childs epilepsy, what are the chance of success with next drug?

Camfield et al conducted this study to determine how often a child's epilepsy is controlled and remits if a first AED fails to control seizures. 17% of patients had inadequate seizure control with their first AED and received a second AED, with only 42% of them having complete remission of their epilepsy. In these children in whom seizures were not controlled with the first AED were more likely to have neurological deficits(p=0.01) and complex partial seizures(p=0.01) and 29% had intractable epilepsy(p<0.0001)

STUDY JUSTIFICATION

Of all the epileptic children, 10 – 20 % have intractable epilepsy. Though intractable epilepsy has been extensively studied in developed countries, there are not many studies done in developing countries. In India, there are some studies done in north India, but not in South India. This study will be useful in identifying children prone for intractability at the earliest, so that we can start treatment accurately.

AIM OF THE STUDY

To find out the predictors of intractable epilepsy in childhood & to identify these children prone for intractability at the earliest

SUBJECTS AND METHODS

Study design:

Case Control Study

Study place:

Dept. of paediatric Neurology, Institute of Child Health & Hospital for Children, Egmore.

Study Period:

2 Years(october 2007 to august 2009)

Study Population:

All epilepsy cases attending neurology OP in the age group 6months to 12 yrs

Sampling technique:

Cases:

Epileptic patients who have seizure frequency of atleast 1 attack per month during 6 months despite receiving 2 antiepileptic drugs with adequate dosage & compliance

Controls:

Children with epilepsy who have complete control of seizure for > 6months with one or two drugs.

Inclusion criteria:

Epileptic children in age group 6 months to 12 years who meets the definition of cases & controls

Exclusion criteria:

People from outstation

Poor compliance

Pseudo intractability

- Inadequate dosage

- Wrong drug for seizure type
- Non epileptic seizure

Study maneuvre

This case control study was conducted in Neurology Department of institute of child health and Hospital for Children, Chennai. Epileptic children in the age group 6 months to 12 years were included in the study. A total of 50 cases and 50 controls were enrolled.

Detailed history and a detailed neurological examination was done in all patients and entered in a prestructured proforma. Seizures were classified using the international classification of epileptic seizures. Electroencephalogram and neuroimaging was performed in all patients to determine etiology and classification of epilepsy. Cranial computed tomography was performed in all patients. MRI scan was not done in some patients in whom CT scan was diagnostic and in a small number of patients who couldn’t afford MRI.

Factors analyzed included the following

1) Details of pharmacotherapy

   Number of drugs, duration after starting two drugs, whether drug dosage is adequate or not, compliance

2) Age at onset of seizures : <1 year or >1 year
3) Type of seizures
4) Frequency of seizures before starting treatment
5) Frequency of seizures after starting two drugs
6) History of birth asphyxia
7) History of neonatal convulsions
8) History of developmental delay
9) History of status epilepticus
10) Presence of microcephaly
11) Presence of focal neurological deficit
12) CT/MRI findings
13) EEG findings

Statistical analysis

Association between factors analyzed and outcome was determined using chi-square test. Odds ratio and 95% confidence interval was calculated using univariate analysis. Multivariate analysis by logistic regression method was done to rule out confounding factors and to find out independent predictors of outcome.

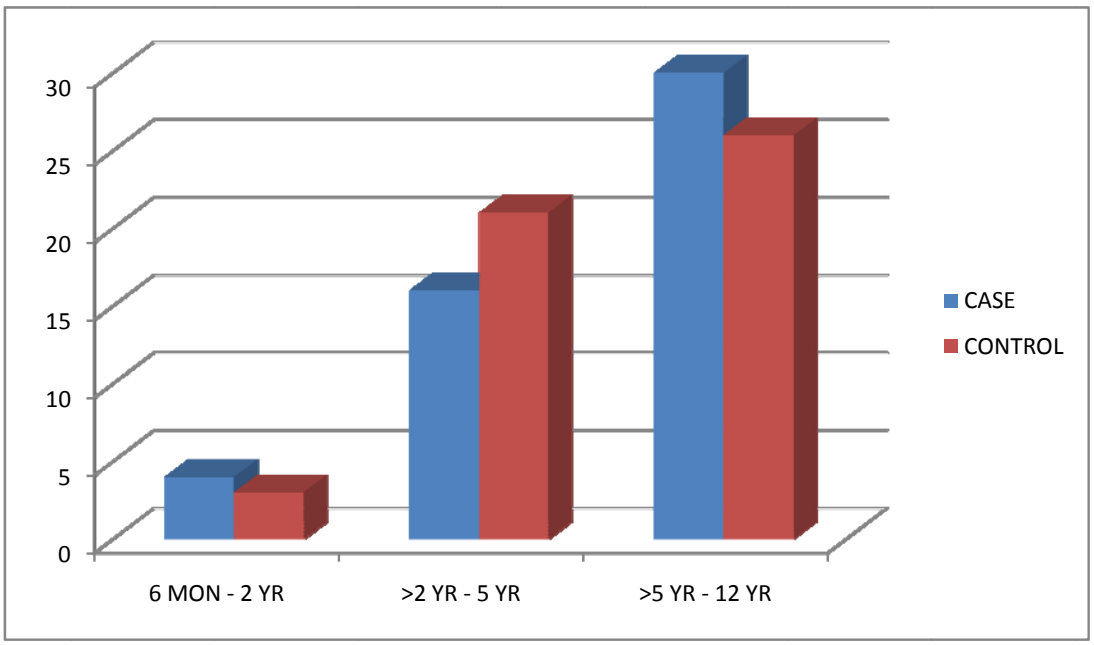
RESULTS

A total of 50 patients with intractable epilepsy and 50 patients with well controlled seizures were studied.

Table-1

Age distribution of study population

Age	case		control	
	number	%	number	%
6 mon – 2 yr	4	8%	3	6%
>2 yr – 5 yr	16	32%	21	42%
>5 yr – 12 yr	30	60%	26	52%
Total	50	100%	50	100%

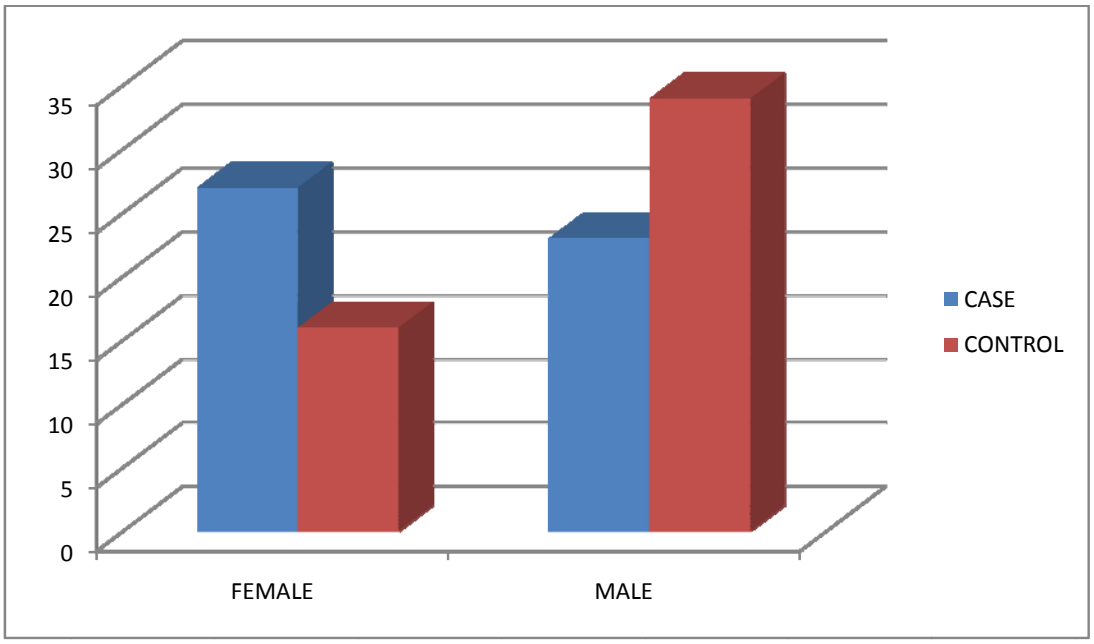


Majority of patients in case group, 30 (60%) belonged to the age group 5 years – 12 years. There were only 4 patients (8%) in 6 months – 2 year age group and 16 patients (32%) belonged to the 2 year to 5 year age group.

Table-2

Sex distribution of study population

Sex	cases		control		p value	odds ratio	95% ci
	n	%	n	%	0.026	2.495	1.105 - 5.629
female	27	54 %	16	32 %			
Male	23	46 %	34	68 %			
Total	50	100 %	50	100 %			

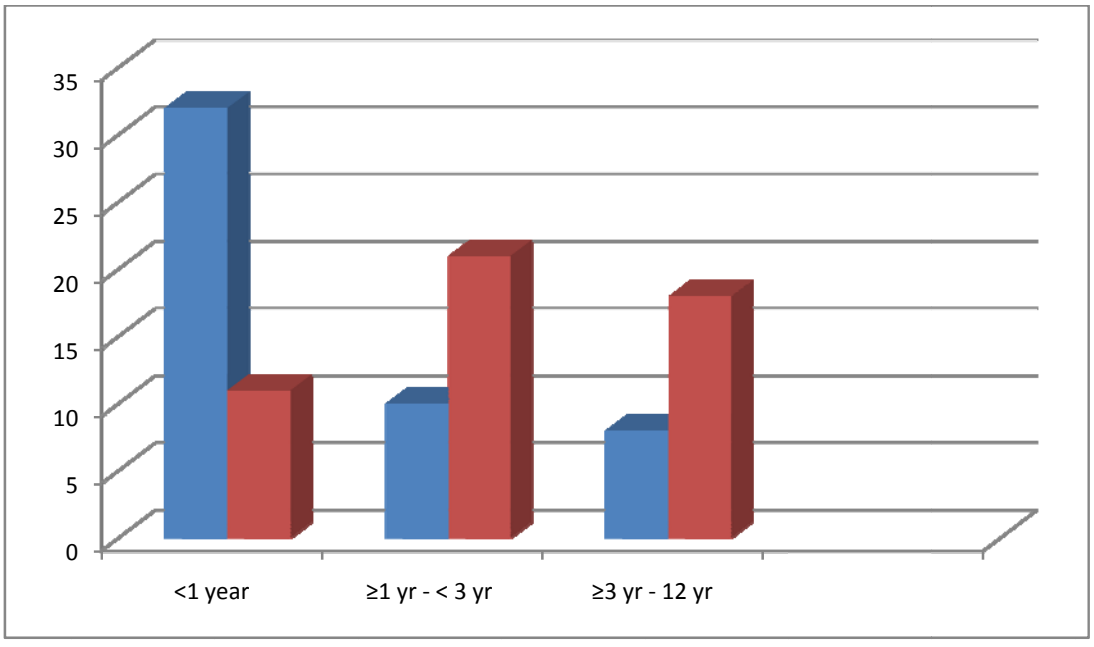


A female preponderance was seen among case group, females constituting 54% and males 46 %. The difference was statistically significant with p value was of 0.026 and odds ratio of 2.495.

Table-3

Age at onset of seizures

age at onset	case		Control	
	n	%	n	%
<1 year	32	64 %	11	22 %
≥1 yr - <3 yr	10	20 %	21	42 %
≥3 yr – 12 yr	8	16 %	18	36 %
total	50	100 %	50	100 %

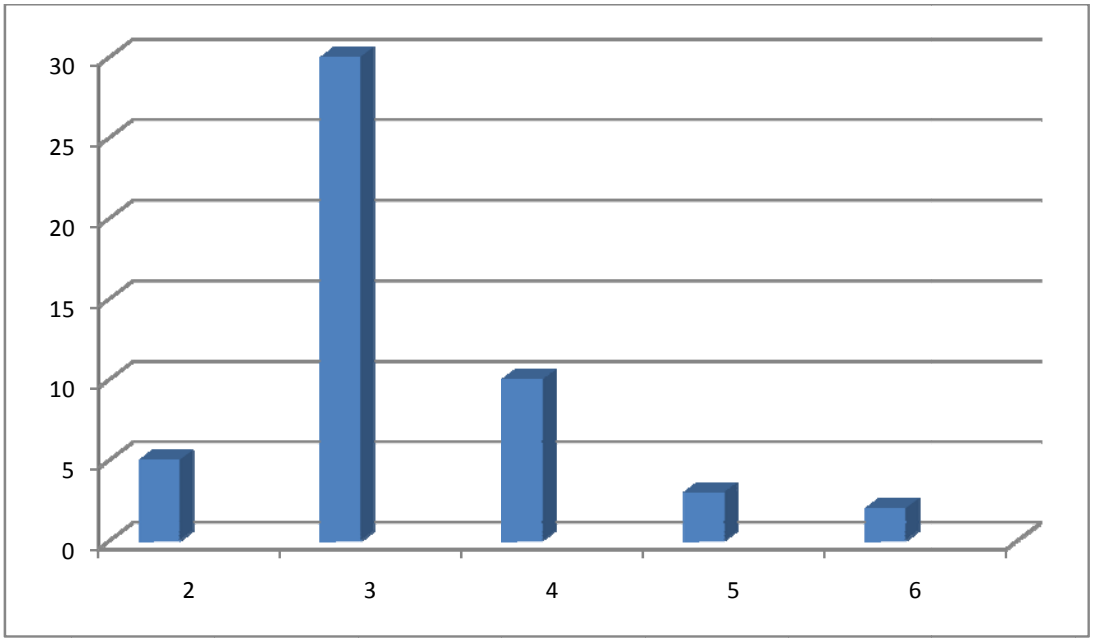


Majority of patients in case group, 32 (64%) had seizure onset < 1 year of age as against patients (22%) in control group. This was found to be statistically significant with a p value of 0.000, Odds ratio of 6.3 and 95% confidence interval of 2.604 to 15.25

Table-4

Number of drugs being taken by case group

no of drugs	Cases	
	N	%
2	5	10 %
3	30	60 %
4	10	20 %
5	3	6 %
6	2	4 %
total	50	100 %

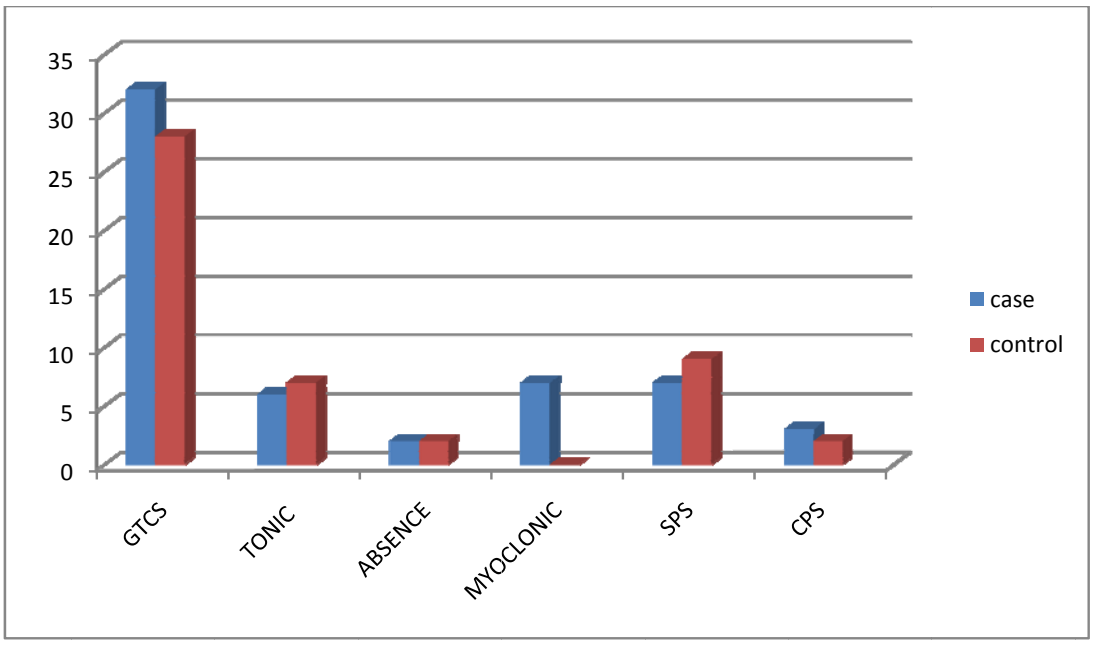


Maximum number of antiepileptic drugs taken was 6 drugs, being taken by two patients. In this study, maximum number of patients with intractable epilepsy, 30 (60 %) were taking three drugs.

Table-5

Type of seizures

seizure type	case		Control	
	n	%	n	%
gtcs	32	64 %	28	56 %
tonic seizures	6	12 %	7	14 %
absence seizures	2	4 %	2	4 %
myoclonic seizures	7	14 %	0	0 %
simple partial seizures	7	14 %	9	18 %
complex partial seizures	3	6 %	2	4 %
mixed	13	26 %	1	2 %



Most common seizure type among cases as well as controls was generalized tonic clonic convulsions (64 % in case group, 56 % in control group). Seven patients (14 %) in case group had myoclonic seizures, where as none among control group had myoclonic seizures. This difference was found to be statistically significant with a p value of 0.006. Mixed seizure type was also found to be more common in case group.

Most of the patients, 34 (68%) in case group had daily seizures, before starting treatment when compared to 8 (16%) in control group. This was found to be statistically significant with a p value of 0.000, odds ratio of 11.15 and 95% confidence interval of 4.26 – 29.18.

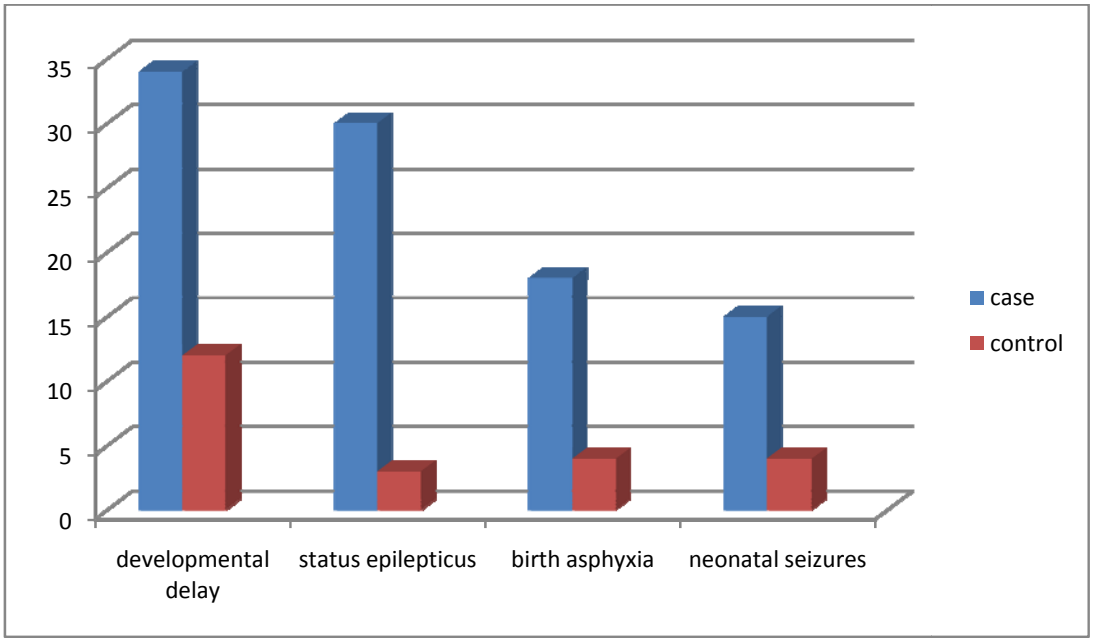
Table-6

Myoclonic seizures

myoclonic seizures	case		control		p value
	n	%	n	%	
yes	7	14%	0	0%	0.006
no	43	86%	50	100%	

Table-7

parameter	case		control		p value	or	95% ci
	n	%	n	%			
developmental delay	34	68 %	12	24 %	0.000	6.72	2.79 – 16.22
h/o status epilepticus	30	60 %	3	6 %	0.000	23.5	6.42 – 85.9
birth asphyxia	18	36 %	4	8 %	0.001	6.46	2.00 – 20.91
neonatal seizures	15	30 %	4	8 %	0.005	4.92	1.50 – 16.15



34 patients (68 %) in case group had developmental delay, against 12 patients (24 %) in control group. (p value – 0.000). 60% of patients with intractable epilepsy had history of status epilepticus whereas only 6 % of patients in control group had status epilepticus (p value = 0.000)

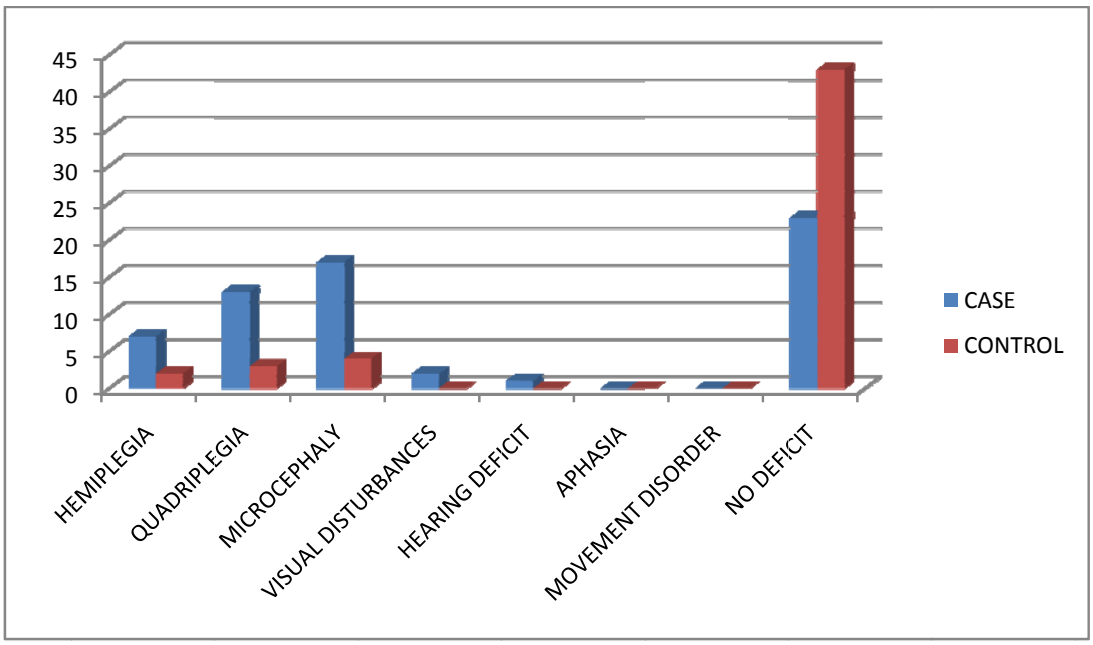
18 patients (36%) with intractable epilepsy had history of birth asphyxia whereas only 4 patients (8%) with well controlled epilepsy had birth asphyxia (p value = 0.001). history of neonatal seizures was found in 15 (30%) cases, as against 4 (8%) controls (p value = 0.005)

Only two patients with intractable epilepsy and four patients with well controlled epilepsy reported some reaction to antiepileptic drug history of febrile seizures was found in 12 % of cases and 18 % of controls

Table-8

Neurological examination

no	examination	case		Control	
		n	%	n	%
1	hemiplegia	7	14 %	2	4 %
2	quadriplegia	13	26 %	3	6 %
3	microcephaly	17	34 %	4	8 %
4	visual disturbances	2	4 %	0	0 %
5	hearing deficit	1	2 %	0	0 %
6	aphasia	0	0 %	0	0 %
7	movement disorder	0	0 %	0	0 %
8	no deficit	23	46 %	43	86 %



Among cases, 7 patients had hemiplegia, 13 patients had quadriplegia, 17 patients had microcephaly and in 23 patients there were no deficit. Presence of microcephaly was found to be statistically significant.

Only 4 cases (8%) and 3 controls (6%) had family history of epilepsy. In both the case and control group, the most common precipitating factor was fever.

Table-9

Neurological examination

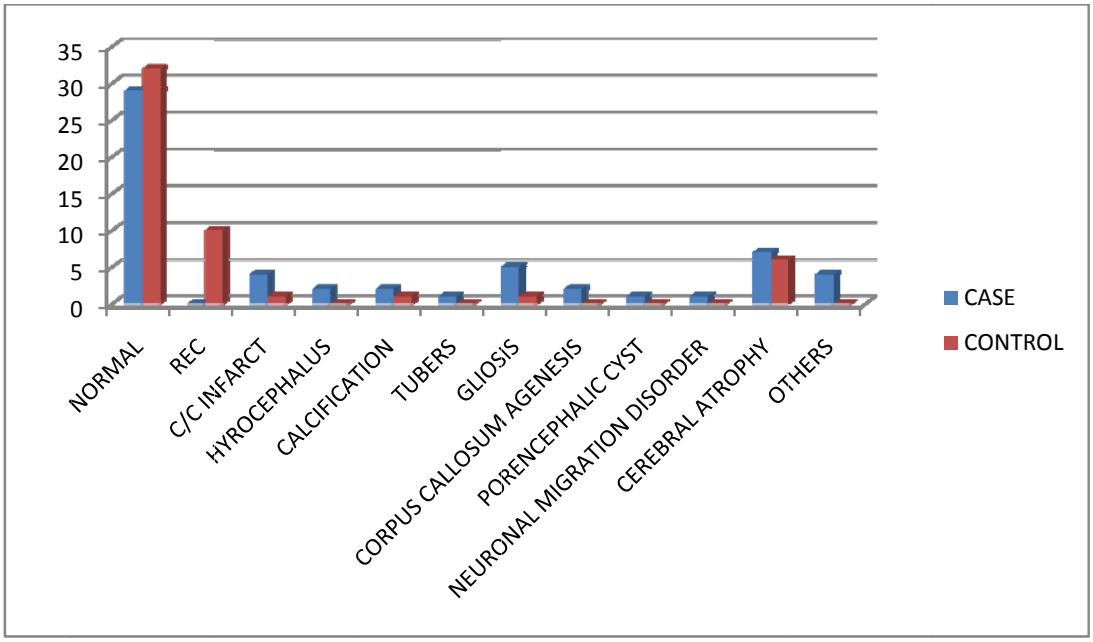
examination	case		Control	
	n	%	n	%
abnormal	27	54 %	7	14 %
normal	23	46 %	43	86 %

Any abnormality detected in neurological examination was to be statistically significant significant with a p value of 0.000

Table-10

CT scan

no	ct scan	case		Control	
		n	%	n	%
1	normal	29	58 %	32	64 %
2	rel	0	0 %	10	20 %
3	chronic infarct	4	8 %	1	2 %
4	hydrocephalus	2	4 %	0	0 %
5	calcification	2	4 %	1	2 %
6	tubers	1	2 %	0	0 %
7	gliosis	5	10 %	1	2 %
8	corpus callosum agenesis	2	4 %	0	0 %
9	porencephalic cyst	1	2 %	0	0 %
10	neuronal migration disorder	1	2 %	0	0 %
11	cerebral atrophy	7	14 %	6	12 %
12	others	4	8 %	0	0 %

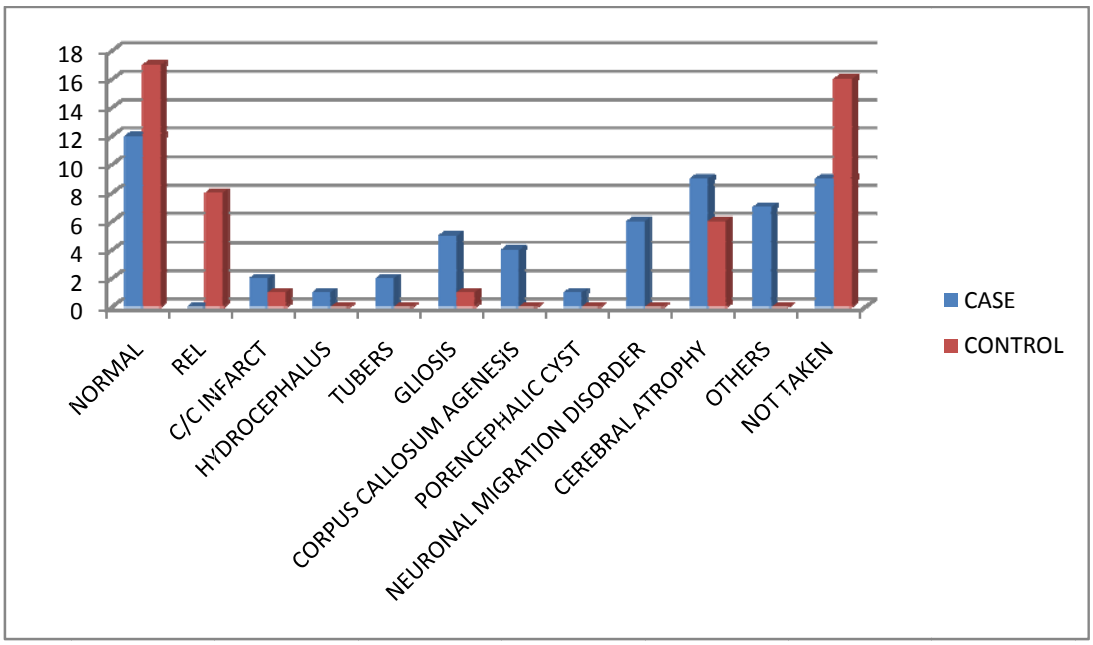


CT Scan was normal in most of the cases 29 (58%). The most common CT abnormality was cerebral atrophy 7 (14%), followed by gliosis 5 (10%)

Table-11

MRI

no	mri	case		Control	
		n	%	n	%
1	normal	12	24 %	17	34
2	rel	0	0 %	8	16
3	c/c infarct	2	4 %	1	2
4	hydrocephalus	1	2 %	0	0
5	tubers	2	4 %	0	0
6	gliosis	5	10 %	1	2
7	corpus callosum agenesis	4	8 %	0	0
8	porencephalic cyst	1	2 %	0	0
9	neuronal migration disorder	6	12 %	0	0
10	cerebral atrophy	9	18 %	6	12
11	others	7	14 %	0	0
12	not taken	9	18 %	16	32



Most common MRI findings were cerebral atrophy 9 (18%) in cases and ring enhancing lesion 8(16%) in controls. The other common MRI findings among case group were neuronal migration disorders 6(12%), corpus callosal agenesis 4(8%) and gliosis 5(10%). MRI was normal in 12 cases and 17 controls

In this study neither CT nor MRI abnormality was found to be statistically significant with intractable epilepsy in the study population.

Table-12

EEG abnormality

no	eeg	case		control	
		n	%	n	%
1	subcortical seizure activity	15	30 %	3	6 %
2	focal seizure activity	2	4 %	5	10 %
3	background abnormality	12	24 %	7	14 %
4	others	4	8 %	2	4 %
5	normal	17	34 %	33	66 %

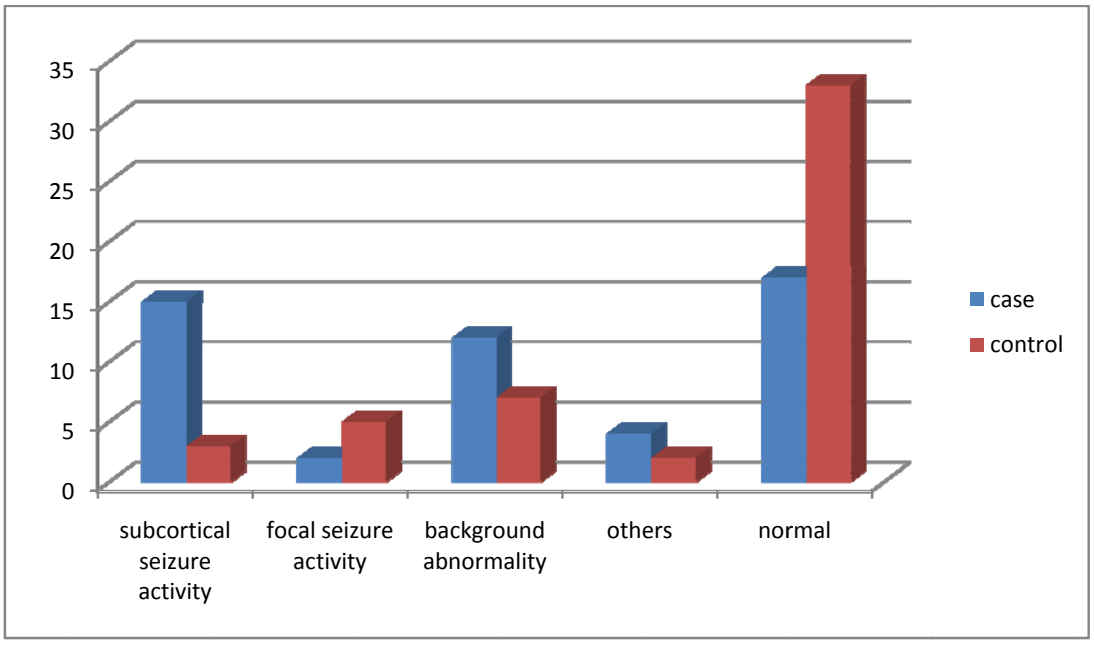


Table-13

EEG abnormality

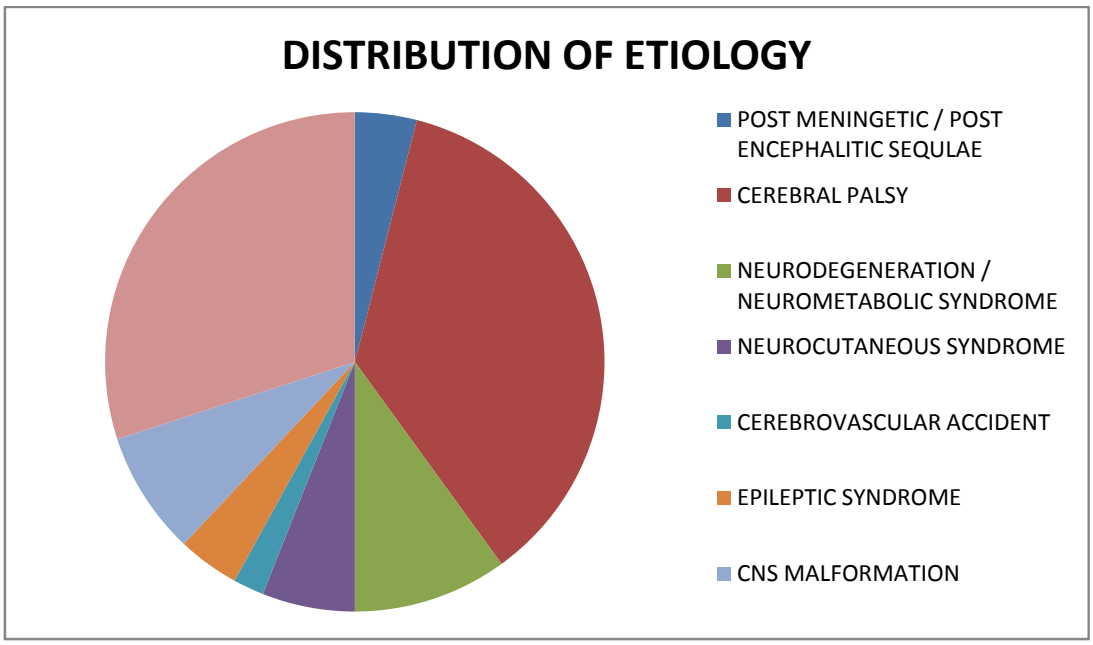
eeg	case		control		p value	or	95 % ci
	n	%	n	%			
abnormal	33	66 %	17	34 %	0.001	3.76	1.64 – 8.62
normal	17	34 %	33	66 %			

The most common EEG abnormality was subcortical seizure activity 15 (30 %) followed by background abnormality 12 (24 %). EEG was normal in 17 (34 %) cases and 33 (66 %) control. EEG abnormality was found to be statistically significant with a p value of 0.001.

Table-14

Distribution of etiology among cases

no	etiology	number	%
1	post meningitic/ post encephalitic sequelae	2	4 %
2	cerebral palsy	18	36 %
3	neurodegeneration/ neurometabolic syndrome	5	10 %
4	neurocutaneous syndrome	3	6 %
5	cerebrovascular accident	1	2 %
6	epileptic syndrome	2	4 %
7	cns malformaton	4	8 %
8	others	15	3 %



Multivariate analysis:

Multivariate analysis was done by multiple logistic regression method to examine association between intractable epilepsy and potential predictive factors. Female sex, multiple seizures before starting treatment, neurological impairment, microcephaly and EEG abnormalities were found to be independent predictors of mortality.

Table-15

Independent predictors of intractable epilepsy after multivariate analysis

Serial number	factor	Standard error	significance	Odds ratio	95% confidence interval
1	sex	0.416	0.017	2.68	1.18-6.07
2	Multiple seizures before treatment	0.502	0.000	9.6	3.61-25.87
3	Neurological impairment	0.698	0.0015	9.2	2.33-36.19
4	microcephaly	0.793	0.0007	14.87	3.13-70.50
5	EEG abnormality	0.439	0.000	5.52	2.33-13.07

DISCUSSION

Intractable epilepsy does not have a common agreed-upon definition. It makes the subject very complex and comparison of results becomes difficult. In our study intractable epilepsy was defined as seizure frequency of atleast one attack per month during six months despite receiving 2 antiepileptic drugs,with adequate dosage and compliance. Definition by Chawla et al[(1)] is similar to our definition. The aim of our study was to find out the predictors of intractable epilepsy in childhood so that early identification of these children prone for intractability is possible. This is essential for selecting patients for more intensive investigations and treatment such as early consideration of epilepsy surgery and for parental counselling.

In this study, majority of cases 60%, patients belonged to the age group 5 years to 12 years. Majority of controls 52%, also belonged to the same age group. Female gender is found to be a risk factor for developing intractable epilepsy in this study, but this is in contrast with the results of Javad akhondian et al [(4)] , where male gender was found to be a risk factor.

Significant association with p value 0.000 was found between age

at onset of seizures less than one year and intractability. This is similar to the results of Chawla et al [1] and Javad Akhondian et al[4].

In our study , generalised seizures were more common than partial seizures among cases as well as controls. Presence of myoclonic epilepsy was associated with intractability with a p value of 0.006. This is in concordance with the results of Javad Akhondian et al[4] and Chawla et al [1]. However Camfield et al [12] didn't find seizure type as a predictor of intractable epilepsy even in univariate analysis. Multiple seizure type before starting treatment was found to be a predictor of intractable epilepsy in our study which is similar to the results of Chawla et al[1] , singhvi et al[5] and Javad Akhondian et al[4] .

In our study 68% of patient of intractable epilepsy had developmental delay which was found to be statistically significant. 36% of patients had history of birth asphyxia in newborn period which was also statistically significant with a p value of 0.001.

We noted , as did Sillanpaa et al[11] that status epilepticus and intractable seizures were strongly associated, partly because children who had symptomatic epilepsy were more likely to have an episode of status epilepticus. This association was also found in the results of berg et al [2]. The odds ratio of 23.5 , suggests that occurrence of status epilepticus may be of some prognostic significance, it may be a marker for an underlying etiology even if none is detected at the time of initial presentation and evaluation.

Neonatal seizures was found to be a predictor of intractable

epilepsy, with a p value of 0.005 with odds ratio of 4.92 and 95% confidence interval of 1.50- 16.15 . This is comparable to the results of Chawla et al [(1)] and Berg et al[(2)] . A history of febrile seizures was not found to be a predictor of intractable epilepsy. Therefore although febrile seizures are a risk factor for epilepsy, our data indicates that they are not associated with poor prognosis if epilepsy develops.

The most common examination finding in our study population was microcephaly (34%) , followed by quadriparesis (26%) and hemiplegia(14%). Abnormal neurological examination was found to be a predictor of intractable epilepsy, similar to the results of Chawla et al [(1)] and Berg et al [(2)] .

CT scan or MRI abnormalities, unlike other studies was not found to be a predictor of intractable epilepsy. The most common CT scan abnormalities detected were cerebral atrophy followed by gliosis. Common MRI findings were cerebral atrophy, neuronal migration disorders& corpus callosal agenesis. EEG abnormality was found to be a predictor of intractable epilepsy, with a p value of 0.001. This is comparable to the results of singhvi et al[(5)] .

Most common cause of intractable epilepsy detected was cerebral palsy found in 18 of patients.3 patients had neurocutaneous syndromes out of which 2 had tuberous sclerosis and one had sturge weber syndrome. 3

patients had neurodegenerative syndrome, 2 patients had neuro metabolic syndrome and 4 patients had neuronal migration disorders. 2 patient had lennox gestaut syndrome and 2 patient had post meningitic sequelae/post encephalitic sequelae. Etiology couldn't be found in 15 patients.

Independent predictors of intractable epilepsy after multiple logistic regression analysis were female sex, multiple seizures before the onset of treatment, neurological impairment, microcephaly and EEG abnormality. Chawla et al study revealed the independent predictors to be neurological impairment, age at seizure onset less than one year, myoclonic seizures and remote symptomatic epilepsy[1] . Sillanpaa et al [5] found that occurrence of status epilepticus, high initial seizure frequency and remote symptomatic etiology were the only independent predictors of seizure intractability

SUMMARY

- Female gender was found to be a risk factor for developing intractable epilepsy.
- Significant association with p value <0.001 was found between age at onset of seizures less than one year and intractable epilepsy.
- Generalized seizures were the most common seizure type in case and control group.
- Presence of myoclonic epilepsy was associated with intractability with a p value of 0.006.
- History of birth asphyxia , neonatal seizures, developmental delay and status epilepticus were also significant risk factors for development of intractable epilepsy.
- The most common examination finding among patients with intractable epilepsy was microcephaly followed by quadriparesis. Abnormal neurological examination was found to be a independent predictor of intractable epilepsy with p value of 0.0015.
- The most common CT abnormality detected were cerebral atrophy followed by gliosis
- Common MRI findings were cerebral atrophy, neuronal migration disorders and corpus callosal agenesis.

- EEG abnormality was found to be a independent predictor of intractability with p value of 0.001
- Most common etiology of intractabile seizures was cerebral palsy seen in 36% of cases, followed by neuronal migration disorders and neurocutaneous syndromes.

CONCLUSION

Factors associated significantly with intractable epilepsy both by univariate and multivariate analysis were female sex, multiple seizures before starting treatment, neurological impairment, microcephaly and EEG abnormality. Early identification of these children prone to develop intractable seizures is critical for parental counselling, selecting patients for more intensive investigations and treatment, such as early consideration for epilepsy surgery.

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PROFORMA

REGISTER NO.

Name :

Age in:

years

Sex :1. Male

2. Female

Address :

Area :1. Rural

2. Urban

Weight in:

Kg

Age of:1. < 1 year

onset of 2. >= 1 – < 3 years

seizures

3. >= 3 – 12 years

Drugs :1.

started 2.

with

3.

Drugs Now:1.

on 2.

:

3.

:

4.

:

No of

drugs:

Duration after starting 2 drugs:		
Response to treatment	:1. Intractable epilepsy 2. Responding to treatment	
History of: any reaction to AED	1. Yes 2. No	
Developme nt	:1. Normal 2. Delayed	
Type of: Seizures	1. Generalised Tonic Clonic Seizures 2. Generalised Tonic seizures 3. Absence 4. Atonic 5. Myoclonic	

6. Simple Partial Seizures
7. Complex Partial Seizures
8. Mixed
9. Others

Frequency of seizures before starting treatment :
1. Daily
2. > 1 / week
3. 1 – 4 / months
4. < 1 / month

Frequency of seizures after starting 2 drug on average in 6 months :
1. 1
2. 2-3
3. 4-5
4. 6-7
5. 8-9
6. >or = 10

History of status epilepticus: 1. Yes 2. No

History Birth Asphyxia: 1. Yes 2. No

History of Neonatal Convulsion: 1. Yes 2. No

History of Febrile Seizures: 1. Yes 2. No

Family History of Epilepsy: 1. Yes 2. No

Precipitatin:

g Factors

1. Fever / Intercurrent infection
2. Lack of Sleep
3. Physical stress
4. Mental Stress
5. Watching TV
6. Others

Etiology of:

Intractable Epilepsy

1. Post Meningitic / Encephalitic Sequelae
2. Neurocysticercosis/REL
3. CP/MR
4. Neurodegenerative syndrome
5. Neurocutaneous syndrome
6. Head injury
7. CVA
8. Epileptic Syndrome
9. CNS Malformation
10. Mesial temporal sclerosis
11. Others

Neurological Examination :

1. Hemiplegia
2. Quadriplegia
3. Visual disturbance
4. Hearing deficit
5. Aphasia
6. Movement disorders
7. Microcephaly
8. No deficit

CT Scan :

1. Normal
2. REL
3. Chronic Infarct
4. Hydrocephalus
5. Calcification
6. Tubers
7. Gliosis
8. Corpus Callosum Agenesis
9. Porencephalic Cyst
10. Neuronal Migration Disorder

11.Cerebral atrophy

12.Others

MRI Scan :1.Normal

2.REL

3.Chronic Infarct

4.Hydrocephalus

5.Calcification

6.Tubers

7.Gliosis

8.Mesial Temporal Sclerosis

9.Corpus Callosum Agenesis

10.Porencephalic Cyst

11.Neuronal Migration Disorder

12.Cerebral atrophy

13.Others

14.Not taken

EEG :1. Subcortical seizure activity

2. Focal seizure activity
3. Background abnormality
4. Others
5. Normal

ABBREVIATIONS

EEG- Electroencephalogram

CT- Computed tomography

MRI- Magnetic resonance imaging

PET- Positron emission tomography

SPECT- Single photon emission computed tomography

IS- Infantile spasm

SE- Status epilepticus

OR- Odds ratio

CI- Confidence interval

GTCS- Generalised tonic clonic convulsions

SPS- Simple partial seizures

CPS- Complex partial seizures

REL- Ring enhancing lesion